

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61L 29/16, 27/54, 31/16, 17/00, 15/44, 2/18 // 101:02, 101:32, 101:34, 101:42	A1	(11) International Publication Number: WO 00/57933 (43) International Publication Date: 5 October 2000 (05.10.00)
(21) International Application Number: PCT/US00/08692 (22) International Filing Date: 30 March 2000 (30.03.00) (30) Priority Data: 09/281,872 31 March 1999 (31.03.99) US (71) Applicant: THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK [US/US]; 116th Street and Broadway, New York, 10027 (US). (72) Inventors: MODAK, Shanta; 184 Howland Avenue, River Edge, NJ 07661 (US). SAMPATH, Lester; 7 Lawrence Street, Nyack, NY 10960 (US). (74) Agents: TANG, Henry et al.; Baker Botts LLP, 30 Rockefeller Plaza, New York, NY 10112-0228 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: TRICLOSAN AND SILVER COMPOUND CONTAINING MEDICAL DEVICES (57) Abstract The present invention relates to polymeric medical articles comprising combinations of triclosan and silver-containing compounds. It is based, at least in part, on the discovery that these agents act synergistically, thereby permitting the use of relatively low levels of both agents. While it had been previously found that triclosan can be particularly useful when used in conjunction with chlorhexidine, it has been further discovered that medical articles having suitable antimicrobial properties may be prepared, according to the present invention, which contain triclosan without chlorhexidine. Such medical articles offer the advantage of preventing or inhibiting infection while avoiding undesirable adverse reactions to chlorhexidine by individuals that may have sensitivity to chlorhexidine.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TRICLOSAN AND SILVER COMPOUND CONTAINING MEDICAL DEVICES

SPECIFICATION

1.0 INTRODUCTION

5 The present invention relates to medical devices comprising synergistic combinations of triclosan and silver containing compounds.

2.0 BACKGROUND OF THE INVENTION

Whenever a medical device comes in contact with a patient, a risk of infection is created. Thus, a contaminated examination glove, tongue depressor, or
10 stethoscope could transmit infection. The risk of infection dramatically increases for invasive medical devices, such as intravenous catheters, arterial grafts, intrathecal or intracerebral shunts and prosthetic devices, which not only are, themselves, in intimate contact with body tissues and fluids, but also create a portal of entry for pathogens.

15 A number of methods for reducing the risk of infection have been developed which incorporate anti-infective agents into medical devices, none of which have been clinically proven to be completely satisfactory. Such devices desirably provide effective levels of anti-infective agent during the entire period that the device is being used. This sustained release may be problematic to achieve, in that a
20 mechanism for dispersing anti-infective agent over a prolonged period of time may be required, and the incorporation of sufficient amounts of anti-infective agent may adversely affect the surface characteristics of the device. The difficulties encountered in providing effective antimicrobial protection increase with the development of drug-resistant pathogens.

25 One potential solution to these problems is the use of a synergistic combination of anti-infective agents that requires relatively low concentrations of individual anti-infective agents which may have differing patterns of bioavailability.

Two well-known anti-infective agents are chlorhexidine and triclosan. The following patents and patent application relate to the use of chlorhexidine and/or triclosan in medical devices.

United States Patent No. 4,723,950 by Lee relates to a microbicidal
5 tube which may be incorporated into the outlet tube of a urine drainage bag. The
microbicidal tube is manufactured from polymeric materials capable of absorbing and
releasing anti-microbial substances in a controllable sustained time release
mechanism, activated upon contact with droplets of urine, thereby preventing the
retrograde migration of infectious organisms into the drainage bag. The microbicidal
10 tube may be produced by one of three processes: (1) a porous material, such as poly-
propylene, is impregnated with at least one microbicidal agent, and then coated with a
hydrophilic polymer which swells upon contact with urine, causing the leaching out of
the microbicidal agent; (2) a porous material, such as high density polyethylene, is
impregnated with a hydrophilic polymer and at least one microbicidal agent; and (3) a
15 polymer, such as silicone, is compounded and co-extruded with at least one
microbicidal agent, and then coated with a hydrophilic polymer. A broad range of
microbicidal agents are disclosed, including chlorhexidine and triclosan, and
combinations thereof. The purpose of Lee's device is to allow the leaching out of
microbicidal agents into urine contained in the drainage bag; similar leaching of
20 microbicidal agents into the bloodstream of a patient may be undesirable.

United States Patent No. 5,091,442 by Milner relates to tubular articles,
such as condoms and catheters, which are rendered antimicrobially effective by the
incorporation of a non-ionic sparingly soluble antimicrobial agent, such as triclosan.
The tubular articles are made of materials which include natural rubber, polyvinyl
25 chloride and polyurethane. Antimicrobial agent may be distributed throughout the
article, or in a coating thereon. A condom prepared from natural rubber latex
containing 1% by weight of triclosan, then dipped in an aqueous solution of chlorhexi-
dine, is disclosed. United States Patents Nos. 5,180,605 and 5,261,421, both by
Milner, relate to similar technology applied to gloves.

30 United States Patents Nos. 5,033,488 and 5,209,251, both by Curtis et
al., relate to dental floss prepared from expanded polytetrafluoroethylene (PTFE) and

coated with microcrystalline wax. Antimicrobial agents such as chlorhexidine or triclosan may be incorporated into the coated floss.

United States Patent No. 5,200,194 by Edgren et al. relates to an oral osmotic device comprising a thin semipermeable membrane wall surrounding a
5 compartment housing a "beneficial agent" (that is at least somewhat soluble in saliva) and a fibrous support material composed of hydrophilic water-insoluble fibers. The patent lists a wide variety of "beneficial agents" which may be incorporated into the oral osmotic device, including chlorhexidine and triclosan.

United States Patent No. 5,019,096 by Fox, Jr., et al. relates to
10 infection-resistant medical devices comprising a synergistic combination of a silver compound (such as silver sulfadiazine) and chlorhexidine.

International Patent Application No. PCT/GB92/01481, Publication No. WO 93/02717, relates to an adhesive product comprising residues of a copolymerisable emulsifier comprising a medicament, which may be povidone iodine, triclosan,
15 or chlorhexidine.

International Patent Application No. PCT/US96/20932, Publication No. WO 97/25085, relates to polymeric medical articles comprising synergistic combinations of chlorhexidine and triclosan which utilize relatively low levels of these agents.

20 In contrast to the present invention, none of the above-cited references teach medical articles comprising synergistic combinations of triclosan and silver compounds which utilize relatively low levels of these agents and provide effective levels of antimicrobial activity, even in the absence of chlorhexidine.

3.0 SUMMARY OF THE INVENTION

25 The present invention relates to polymeric medical articles comprising combinations of triclosan and/or other chlorinated phenols and silver-containing compounds. It is based, at least in part, on the discovery that these agents act synergistically, thereby permitting the use of relatively low levels of both agents. While it had been previously found that triclosan can be particularly useful when used
30 in conjunction with chlorhexidine, it has been further discovered that medical articles

having suitable antimicrobial properties may be prepared, according to the present invention, which contain triclosan and a silver compound without chlorhexidine. Such medical articles offer the advantage of preventing or inhibiting infection while avoiding undesirable adverse reactions to chlorhexidine by individuals that may have a sensitivity to chlorhexidine, such as a chlorhexidine allergy.

The present invention is also based, at least in part, on the discovery that the surface of medical articles, especially catheters, impregnated with triclosan and silver compounds generally were found to be smoother and shinier in comparison with catheters impregnated with triclosan and chlorhexidine. Even when the triclosan-silver compound impregnated catheters exhibited commensurate or smaller zones of inhibition compared to triclosan-chlorhexidine catheters, there was little or no bacterial adherence observed on the former when exposed to bacterial culture. Microbial adherence on the surfaces of medical devices are the result of a deposition of fibrinogen and fibronectin on the surface which forms a host biofilm. Because bacteria tend to adhere to this biofilm, glycocalyx forms which serves as a bacterial reservoir causing blood stream infections. Without being bound by any particular theory, it is believed that medical articles of the invention, by virtue of their smooth surfaces, may be less physically irritating than prior art devices, may be less likely to provoke fibrinogen and/or fibronectin deposition, and therefore may avoid bacterial colonization.

4.0 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to medical articles comprising combinations of triclosan and/or another chlorinated phenol and one or more silver-containing compound (hereafter, "silver compound").

While not being bound or limited by any particular theory, it is believed that the combination of triclosan and a silver compound forms a soluble complex. This would explain observations, such as those set forth in Example Section 5 below, that the presence of triclosan improves the solubility of various silver compounds, thereby improving their bioavailability.

As shown in Example Sections 7, 9-17 and 19, medical articles, which may be hydrophilic or hydrophobic, treated with combinations of triclosan and various silver compounds exhibit desirable antimicrobial properties. As shown in Example Sections 8, 13 and 14 such articles exhibit smooth surfaces that tend to resist bacterial adherence, which may be at least partly responsible for their antimicrobial quality.

The present invention provides for medical articles treated with chlorinated phenols other than triclosan in combination with one or more silver compound. As shown in Example Section 18, such combinations result in enhanced antimicrobial activity. Suitable chlorinated phenols include parachlorometaxylenol ("PCMX") and dichlorometaxylenol ("DCMX"). The amount of chlorinated phenol which may be used is as set forth below for triclosan, but may be adjusted for differences in potency when tested against a particular microbe. For example, in specific, non-limiting embodiments of the invention polymeric medical articles may be prepared using treatment solutions comprising between about 0.1 and 5 percent, preferably between about 0.3 and 1.5 percent, of a silver compound, and between about 0.1 and 20 percent, preferably between about 0.1 and 8 percent, of a chlorinated phenol, preferably PCMX. The present invention also provides for medical articles comprising triclosan in addition to another chlorinated phenol.

In additional embodiments, the present invention provides for medical articles having anti-infective activity which comprise triclosan and/or another chlorinated phenol, a silver compound, and an anti-inflammatory agent. It has been found that the addition of an anti-inflammatory compound enhances the antimicrobial activity of such devices (see Section 17 below).

In still further embodiments, the present invention provides for medical articles which have been treated with a hydrogel, and further comprise a metal compound.

The term triclosan ("TC"), as used herein, refers to a compound also known as 2,4,4'-trichloro-2'-hydroxydiphenyl ether and also known as 5-chloro-2-(2,4-dichlorophenoxy)phenol.

The term silver compound, as used herein, refers to a compound comprising silver, either in the form of a silver atom or a silver ion unlinked or linked to another molecule via a covalent or noncovalent (*e.g.*, ionic) linkage, including but not limited to covalent compounds such as silver sulfadiazine ("AgSD") and silver salts such as silver oxide ("Ag₂O"), silver carbonate ("Ag₂CO₃"), silver deoxycholate, silver salicylate, silver iodide, silver nitrate ("AgNO₃"), silver paraaminobenzoate, silver paraaminosalicylate, silver acetylsalicylate, silver ethylenediaminetetraacetic acid ("Ag EDTA"), silver picrate, silver protein, silver citrate, silver lactate and silver laurate.

The terms "medical article" and "medical device" are used interchangeably herein. Medical articles that may be treated according to the invention are either fabricated from or coated or treated with biomedical polymer (and hence may be referred to as "polymer-containing medical articles") and include, but are not limited to, catheters including urinary catheters and vascular catheters (*e.g.*, peripheral and central vascular catheters), wound drainage tubes, arterial grafts, soft tissue patches (such as polytetrafluoroethylene ("PTFE") soft tissue patches), gloves, shunts, stents, tracheal catheters, wound dressings, sutures, guide wires and prosthetic devices (*e.g.*, heart valves and LVADs). Vascular catheters which may be prepared according to the present invention include, but are not limited to, single and multiple lumen central venous catheters, peripherally inserted central venous catheters, emergency infusion catheters, percutaneous sheath introducer systems and thermodilution catheters, including the hubs and ports of such vascular catheters. The present invention may be further applied to medical articles that have been prepared according to United States Patent No. 5,019,096 by Fox, Jr. et al..

The following are descriptions of particular embodiments of the invention.

Percentages recited herein refer to weight/volume (w/v), except as indicated otherwise.

The present invention provides, in various non-limiting embodiments, for: (1) treatment solutions comprising between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent of a silver compound; and between

about 0.1 and 20 percent and preferably between about 0.1 and 8 percent of triclosan and/or other chlorinated phenol; (2) treatment solutions comprising between about 0.1 and 10 percent, and preferably between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer; between about 0.1 and 5 percent, and preferably
5 between about 0.3 and 1.5 percent of a silver compound; and between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent of triclosan and/or other chlorinated phenol; (3) polymer-containing medical articles treated with a treatment solution as set forth in (1) or (2) above, and articles physically equivalent thereto (that is to say, articles prepared by a different method but having essentially the same
10 elements in the same proportions); (4) polymer-containing medical articles treated with treatment solutions set forth in (1) or (2) above wherein the articles are dried and thereafter coated with an anti-infective and/or polymeric coating in accordance with a two-step process. The treatment solutions set forth in (1) or (2) may optionally further comprise (i) an organic acid, at a concentration of between about 0.1 and 5 percent,
15 preferably between about 0.1 and 2 percent; (ii) an anti-inflammatory agent, at a concentration of between about 1 and 5 percent, preferably between about .1 and 1 percent; (iii) an antimicrobial other than a silver compound or triclosan at a concentration of between about 0.1 and 10 percent; and/or (iv) a hydrogel at a concentration of between about 0.5 to 10 percent, preferably between about 1 and 5
20 percent. In preferred non-limiting embodiments of the invention, the amount of silver present as silver atom or silver ion is about 0.9%. In preferred non-limiting embodiments of the invention, the treatment solution and/or medical article does not contain chlorhexidine or a chlorhexidine salt. The medical articles are "treated" by exposing them, for an effective period of time, to the treatment solution, where an
25 "effective period of time" is that period of time sufficient to introduce anti-infective quantities of triclosan and/or other chlorinated phenol and silver compound. Where the concentration of triclosan and/or other chlorinated phenol in the treatment solution is between 0.1 and 8 percent, the effective period of time may be between about 30 seconds and one hour; where the concentration of tricolsan and/or other chlorinated
30 phenol in the treatment solution is between about 9 and 20 percent, the effective period of time may be between about 10 seconds and 2 minutes. Longer periods of

exposure may be used provided that undesirable deterioration of the medical article does not occur.

The term "about" indicates a variation within 20 percent.

In particular non-limiting embodiments of the invention, where the
5 medical article is a vascular catheter, such as a central venous catheter, the amount of triclosan contained is about 100-600 $\mu\text{g}/\text{cm}$, preferably about 400-500 $\mu\text{g}/\text{cm}$ and the amount of silver atom or ion is 25 to 100 $\mu\text{g}/\text{cm}$, preferably 30 to 80 $\mu\text{g}/\text{cm}$.

Medical articles prepared according to the invention may be treated on their external surface, internal surface, or both. For example, and not by way of
10 limitation, where the medical article is a catheter, the internal surface and/or external surface of the catheter may be treated according to the invention. For example, where it is desired to treat both internal and external surfaces, an open-ended catheter may be placed in a treatment solution such that the treatment solution fills the catheter lumen. If only the external surface is to come in contact with treatment solution, the ends of
15 the catheter may be sealed before it is placed in the treatment solution. If only the internal surface is to come in contact with treatment solution, the solution may be allowed to pass through and fill the lumen but the catheter is not immersed in the treatment solution.

Medical articles may be dipped, soaked, or otherwise have a surface
20 coated. The term "dipped" suggests briefer exposure to treatment solution relative to soaking, and preferably is for a period of time less than fifteen minutes.

Successful treatment of a medical article with a polymer comprising an anti-infective agent may be problematic, particularly where the medical article has a hydrophobic surface. The adherence of the polymer may depend upon (1) the
25 polymeric matrix in which the anti-infective agent is suspended; (2) compatibility (or lack thereof) between the agent-polymeric matrix and the surface of the article; (3) the solvent system; and (4) the thickness of polymer/anti-infective agent desirably applied. Furthermore, the rates of release of various anti-infective agents from diverse polymers may differ. To address these issues, the present invention provides
30 for two different methods for treating medical articles: a one-step method, and a two-step method, both of which are set forth below.

Polymers, triclosan, and silver compounds used according to the invention may be sparingly soluble in certain solvents or solvent mixtures. It therefore may be desirable to first dissolve the relevant material in a solvent or component of a solvent system which favors dissolving. For example, where polyurethane, triclosan, and a silver compound are desirably incorporated into an alcohol/tetrahydrofuran ("THF") solvent system, the polyurethane may first be dissolved in THF and the triclosan and silver compound may be dissolved in alcohol (in certain instances with the addition of an aqueous solution of ammonia (referred to interchangeably herein as either ammonia, ammonium hydroxide, or NH_3) to facilitate solubilization of the silver compound), before the THF and alcohol components are mixed. The use of a solvent system comprising ammonia may be particularly desirable when a silver salt is used.

4.1 HYDROPHILIC ARTICLE TREATED WITH A SOLUTION OF A HYRDOPHILIC POLYMER

In one particular set of non-limiting embodiments, the present invention provides for a hydrophilic polymeric medical article (*i.e.*, a medical article fabricated from a hydrophilic polymer) treated by coating, dipping or soaking the article in a treatment solution of a hydrophilic polymer comprising a silver compound and triclosan (and/or other chlorinated phenol) wherein the silver compound and triclosan or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective anti-microbial activity. The term "effective antimicrobial activity" refers to an ability to decrease the number of colony-forming units of a bacterium or yeast, in a 24 hour period, by a factor of ten or more and preferably a factor of 100 or more. The terms "treat", "treated", etc., as used herein, refer to coating, impregnating, or coating and impregnating a medical article with anti-infective agent. The term "hydrophilic polymer", as used herein, refers to polymers which have a water absorption greater than 0.6 percent by weight (and, in preferred embodiments, less than 2 percent by weight; as measured by a 24 hour immersion in distilled water, as described in ASTM Designation D570-81) including, but not limited to biomedical polyurethanes (*e.g.*, ether-based polyurethanes and ester-based polyurethanes, as set forth in Baker, 1987, in *Controlled Release of Biologically*

Active Agents, John Wiley and Sons, pp. 175-177 and Lelah and Cooper, 1986, *Polyurethanes in Medicine*, CRC Press, Inc., Fla. pp. 57-67; polyurethanes comprising substantially aliphatic backbones such as Tecoflex™ 93A; polyurethanes comprising substantially aromatic backbones such as Tecothane™; and Pellethane™),
5 polyactic acid, polyglycolic acid, natural rubber latex, and gauze or water-absorbent fabric, including cotton gauze and silk suture material. In specific, non-limiting embodiments, the hydrophilic medical article is a polyurethane catheter which has been treated with (*e.g.*, coated, dipped or soaked in) a treatment solution comprising
10 (i) between about 0.1 and 10 percent, and preferably between about 1 and 5 percent, of one or more biomedical polyurethane; (ii) between about 0.1 and 5 percent, and preferably between 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

15 4.2. HYDROPHILIC ARTICLE TREATED WITH A SOLUTION OF A HYDROPHOBIC POLYMER

In another set of particular non-limiting embodiments, the present invention provides for a hydrophilic polymeric medical article treated by coating, dipping or soaking the article in a treatment solution of a hydrophobic polymer comprising a silver compound and triclosan (and/or other chlorinated phenol),
20 wherein the silver compound and triclosan and/or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective anti-microbial activity. The term "hydrophobic polymer", as used herein, refers to a polymer which has a water absorption of less than 0.6% and includes, but is not limited to, silicone polymers such as biomedical silicones (*e.g.*, Silastic Type A) or
25 elastomers (*e.g.*, as set forth in Baker, 1987, in *Controlled Release of Biologically Active Agents*, John Wiley and Sons, pp. 156-162), Dacron, polytetrafluoroethylene ("PTFE", also "Teflon"), polyvinyl chloride ("PVC"), cellulose acetate, polycarbonate, and copolymers such as silicone-polyurethane copolymers (*e.g.*, PTUE 203 and PTUE 205 polyurethane-silicone interpenetrating polymer). In one specific,
30 non-limiting embodiment, the medical article is a polyurethane catheter which has been dipped or soaked in a treatment solution comprising (i) between about 0.1 and 10

percent, and preferably between about 1 and 5 percent, of a polyurethane - silicone copolymer; (ii) between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

4.3 HYDROPHOBIC ARTICLE TREATED WITH A SOLUTION OF A HYDROPHOBIC POLYMER

In another set of particular non-limiting embodiments, the present invention provides for a hydrophobic polymeric medical article treated by coating, dipping or soaking the article in a treatment solution of hydrophobic polymer comprising a silver compound and triclosan and/or other chlorinated phenol, wherein the silver compound and triclosan and/or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective antimicrobial activity. In one specific, non-limiting embodiment, the medical article is a silicone catheter or a polyvinylchloride catheter which has been dipped or soaked in a treatment solution comprising (i) between about 0.1 and 10 percent, and preferably between about 1 and 5 percent, of a silicone polymer; (ii) between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

4.4 HYDROPHOBIC ARTICLE TREATED WITH A SOLUTION OF A HYDROPHILIC POLYMER

In yet another set of particular non-limiting embodiments, the present invention provides for a hydrophobic polymeric medical article treated by coating, dipping or soaking the article in a treatment solution of hydrophilic polymer comprising a silver compound and triclosan and/or other chlorinated phenol, wherein the silver compound and triclosan and/or other chlorinated phenol are present in amounts such that their combination, in the treated article, has effective anti-microbial activity. In a specific, non-limiting embodiment, the medical article is a silicone catheter or Teflon graft which has been dipped, coated or soaked in a treatment

solution comprising (i) between about 0.1 and 10 percent, and preferably between about 1 and 5 percent, of a biomedical polyurethane polymer; (ii) between about 0.1 and 5 percent, and preferably between about 0.3 and 1.5 percent, of a silver compound; and (iii) between about 0.1 and 20 percent, and preferably between about 0.1 and 8 percent, of triclosan and/or other chlorinated phenol.

4.5 MEDICAL ARTICLES IMPREGNATED WITH TRICLOSAN AND A SILVER COMPOUND BY A ONE-STEP METHOD

According to the one-step method of the invention, a polymeric medical article may be treated with a solution comprising one or more silver compounds, triclosan and/or other chlorinated phenol, and optionally containing a biomedical polymer, dissolved in one or more solvents, wherein the solvent(s) selected is (are) capable of swelling the polymeric medical article to be treated; such a solution is referred to herein as an "impregnating solution" (which is a species of treatment solution), and the process by which the article is treated with triclosan and a silver compound is referred to as "impregnation". Suitable solvents include, but are not limited to, tetrahydrofuran ("THF"), dichloromethane, carbon tetrachloride, methanol, ethanol, methyl ethyl ketone, heptane, M-Pyrol and hexane, and mixtures thereof. The term "reagent alcohol" as used herein refers to a solution containing essentially 5% v/v methanol, 5% v/v isopropanol, and 90% v/v ethanol. The biomedical polymer may be hydrophilic or hydrophobic, and includes the various polymers set forth above.

If a hydrophilic polymeric medical article is to be impregnated with a silver compound and triclosan and/or other chlorinated phenol, the impregnating solution may, in specific non-limiting embodiments, comprise the following (percentages of solvents in this paragraph being volume/volume (v/v) except where noted to be weight/volume (w/v)): 95% ethanol/5% water; 95% reagent alcohol/5% water; 70% ethanol/30% water; 70% reagent alcohol/30% water; 50% ethanol/50% water; 50% reagent alcohol/50% water; 30% ethanol/ 70% THF; 30% reagent alcohol/70% THF; 30% methanol/70% THF; 10% ethanol/10% ammonia/80% THF; 10% reagent alcohol/10% ammonia/80% THF; 90% ethanol/10% THF; 90% reagent alcohol/10% THF; 90% methanol/10% THF; 100% ethanol or 100% reagent alcohol.

The treatment solutions may comprise between about 0.1 and 10 percent (w/v), and preferably between about 1 and 5 percent (w/v), of one or more dissolved polymer (e.g., one or more species of polyurethane, silicone, or hydrogel). Preferred soaking times according to the one-step method vary between 15 seconds and 1 hour, depending upon the polymer selected. A shorter soaking time in a drug/solvent system is preferred since it is less likely to negatively affect the physical integrity of the polymeric device, particularly polyurethane catheters. In order to attain a sufficient drug uptake using a shorter soaking time, it is preferred that the amount of triclosan or other chlorinated phenol in the treatment solution be between about 10 and 20 percent (w/v). For a specific example of a method that uses higher levels of triclosan and a shorter soaking time see Section 9 below.

If a hydrophobic polymeric medical article is to be impregnated with a silver compound and triclosan and/or other chlorinated phenol, the impregnating solution may, in specific non-limiting embodiments, comprise the following (percentages of solvents in this paragraph being volume/volume (v/v) except where noted to be weight/volume (w/v)): 10% methanol /90% THF; 10% ethanol/90% THF; 10% reagent alcohol/90% THF; 10% ethanol/10% ammonia/80% THF; 10% reagent alcohol/10% ammonia/80% THF; 30% ethanol/70% THF; 30% reagent alcohol/70% THF; 30% methanol/70% THF; 1-5 percent (w/v) silicone polymer in 10% methanol/90% THF; 1-5 percent (w/v) silicone polymer in 10% ethanol/90% THF; 1-5 percent (w/v) silicone polymer in 10% reagent alcohol/90% THF; 1-2 percent (w/v) polylactic acid in 10% methanol/90% THF; 1-2 percent w/v polylactic acid in 10% ethanol/90% THF; 1-2 percent (w/v) polylactic acid in 10% reagent alcohol/90% THF; 1-5 percent (w/v) silicone polymer in 30% methanol/70% THF; 1-5 percent (w/v) silicone polymer in 30% ethanol/70% THF; 1-5 percent (w/v) silicone polymer in 30% reagent alcohol/70% THF; 1-2 percent (w/v) polylactic acid in 30% methanol/70% THF; 1-2 percent (w/v) polylactic acid in 30% ethanol/70% THF; 1-2 percent (w/v) polylactic acid in 30% reagent alcohol/70% THF; 1-5 percent (w/v) silicone polymer in 100% methyl ethyl ketone; and 1-2 percent (w/v) polyurethane in 30% ethanol/70% THF. In general, such treatment solutions may comprise between 0.1 and 10 percent, and preferably between about 1 and 5 percent, of one or more

dissolved polymer. For specific examples, see Sections 11-12, below, and Section 10, which shows examples of hydrophilic medical articles (*e.g.*, latex urinary catheters) or hydrophobic medical articles (*e.g.*, PTFE soft tissue hernia graft patches) impregnated with triclosan and silver using a solution without polymer.

5 The medical article, or a portion thereof, may be immersed in the impregnating solution to swell, after which the article may be removed and dried at room temperature until all solvent has evaporated and the article is no longer swollen. Other methods may also be used, such that a substantially uniform coat of
10 impregnating solution is applied. During the swelling process, triclosan or other chlorinated phenol and silver compound (and small amounts of polymer when present in the impregnating solution) may be distributed within the polymeric substrate of the article; during drying, the triclosan or other chlorinated phenol and silver compound and biomedical polymer (where present) may migrate somewhat toward the surface of the article. In the case of PTFE devices, no apparent swelling occurs, however, the
15 drugs are trapped in the interstices of the substrate. After drying, the article may be rinsed in either water or alcohol and wiped to remove any excess triclosan or other chlorinated phenol, silver compound, and/or polymer at the surface. This may leave a sufficient amount of triclosan or other chlorinated phenol and silver compound just below the surface of the article, thereby permitting sustained release over a prolonged
20 period of time.

4.6 TWO-STEP METHOD OF PREPARING ANTI-INFECTIVE MEDICAL ARTICLES

 According to the two-step method of the invention, the one-step method may be used to impregnate a medical article with triclosan and/or other
25 chlorinated phenol and a silver compound, and then the medical article may be dipped into a second treatment solution containing triclosan and/or other chlorinated phenol and/or a silver compound and/or one or more polymer, and dried. This method forms a coating on the article and further controls the rate of release of triclosan or other chlorinated phenol and silver compound. For a non-limiting specific example, see
30 Section 7, below.

4.7 MEDICAL ARTICLES HAVING ANTI-ADHERENT PROPERTIES

It has been discovered that medical articles treated with mixtures of silver compounds and triclosan exhibit anti-adherent qualities and anti-microbial effectiveness, even in the absence of chlorhexidine. While not being bound to any particular theory, it is believed that triclosan and silver compounds form a triclosan-silver compound complex, such that impregnation of this triclosan-silver compound complex into medical articles increases resistance to microbial adherence to the surfaces by rendering the surfaces smooth and shiny. It has further been discovered that the combination of silver compounds and other compositions, such as other chlorinated phenolic compounds, anti-inflammatory agents, hydrophilic and hydrophobic polymers and hydrogels each separately contribute to enhanced and prolonged antimicrobial efficacy of the antimicrobial agents. The synergistic combinations of triclosan and silver compounds that are sparingly soluble are especially suitable for forming a smooth surface and for providing a sustained and prolonged release of anti-microbial agents.

In a specific example of a method of direct impregnation of triclosan and a silver compound into a Dacron device, a treatment solution may be prepared including 1 to 6 percent triclosan and 0.1 to 0.2 percent of a silver compound in a solvent mixture containing (v/v) 10 percent ammonia, 10 percent alcohol and 80 percent THF. The device may be soaked for 1 to 10 minutes, dried and rinsed. In variations of this example, between about 1 and 10 percent of a hydrophilic polymer or a hydrophobic polymer may be included in the treatment solution. Suitable hydrophilic polymers include, but are not limited to, one or more of polyurethane, polycaprolactone, and polyactic acid. Suitable hydrophobic polymers include, but are not limited to, silicone polymers.

4.8 MEDICAL ARTICLES COMPRISING TRICLOSAN, A SILVER COMPOUND, AND AN ANTI-INFLAMMATORY AGENT

Anti-inflammatory agents such as salicylic acid, paraaminosalicylic acid, and acetylsalicylic acid were impregnated along with triclosan and a silver compound into medical devices to reduce inflammatory reaction around the wound at the insertion site and thus enhance wound healing. Surprisingly, it has been

discovered that incorporation of these anti-inflammatory agents along with the triclosan and a silver compound enhances the anti-microbial activity of the composition. Since the anti-inflammatory agents do not give zones of inhibition when used alone, it appears that increased zone sizes, observed when the anti-inflammatory agents are added to the triclosan and silver compound combination, is not a result of an additive effect but rather due to potentiation of the activity of the complex. Thus, the present invention provides for medical articles treated with treatment solutions comprising triclosan and/or other chlorinated phenol, a silver compound, and an anti-inflammatory agent, such as salicylic acid or a derivative thereof. In further non-limiting embodiments, the treatment solution may also include an additional anti-infective agent such as those set forth below, or chlorhexidine, or a chlorhexidine salt (at a concentration of between about 0.1 and 5 percent).

4.9 ADDITION OF OTHER ANTI-INFECTIVE AGENTS

Because a major route of entry of pathogens during implantation of medical devices occurs at the insertion site and occurs at the time of implantation, it is important to have an effective broad spectrum antimicrobial field around the device during implantation. In order to enhance the antimicrobial field around a device, antibiotic and anti-microbial agents may be added to medical articles comprising triclosan or other chlorinated phenol and a silver compound including, but not limited to, macrolides, aminoglycosides, penicillins, cephalosporins, quinolones, antifungal agents, chlorhexidine or biguanides other than chlorhexidine, chlorinated phenols, sulfonamides, quarternary ammonium compounds, picloxydine, phenolic compounds (*e.g.*, orthophenylphenol), and polymeric quarternary ammonium compounds. Examples of specific agents which can be used include rifampicin, gramicidin, gentamycin, fusidic acid, miconazole, norfloxacin, polymixin, sulfamylon, furazolidine, alexidine, octenidine hydrochloride, cetrимide, polyhexamethylene biguanide, triclocarban, benzalkonium chloride, iodine and iodine complexes such as povidone iodine, pluronic-iodine complex, benzoic acid, sorbic acid, and ethylenediamine tetraacetic acid (EDTA).

These agents used in addition to the triclosan and/or other chlorinated phenol and silver compound combination provide an effective broad spectrum anti-microbial field of activity initially, which inactivates pathogens that otherwise can heavily contaminate the sterile field during implantation. For a non-limiting specific example, see Section 15.

The anti-adherent surface of these devices continues to prevent adherence of microbes that may enter the device tract during and subsequent to implantation. Once these additional agents are diffused out of the devices, the anti-adherent surface continues to prevent adherence of microbes which may contact the device surface through hematogenous seeding or contaminated infusate. Further, without being bound to any particular theory, it is believed that sustained and prolonged release of the anti-microbial agents occurs from the putative triclosan-silver compound complex which provides a longer period of protection.

4.10 MEDICAL ARTICLES COMPRISING A HYDROGEL

According to the present invention, it has been determined that the use of hydrogel polymers increases the antimicrobial efficacy of hydrophilic or hydrophobic matrix systems. In a particular embodiment, the present invention provides for a hydrophilic or hydrophobic medical article which has been impregnated, coated or impregnated and coated with a treatment solution comprising (i) a hydrophilic or hydrophobic polymer, (ii) one or more metal compounds comprising metal atoms or ions or complexes comprising a metal atom or ion selected from the group consisting of silver, copper, zinc, calcium, aluminum and magnesium, (iii) triclosan or other chlorinated phenol, and (iv) a hydrogel. Such medical articles may further comprise, or the treatment solution may comprise, a biguanide such as chlorhexidine or a chlorhexidine salt. In other embodiments, the present invention provides for a metallic or ceramic medical article coated with a treatment solution of (i) to (iv) as set out above. In a preferred embodiment, the hydrogel comprises polyvinyl pyrrolidone ("PVP"). In another preferred embodiment, the hydrophobic polymer polyvinyl chloride ("PVC") may be used to create a hydrophobic matrix into which PVP and antimicrobial agents may be impregnated. Other useful hydrogels that

may be used to promote enhanced antimicrobial efficacy include polyethylene oxide, pluronics, ethyl and methyl cellulose, hydroxy ethyl and hydroxy methyl cellulose, inicroquats, and polyhydroxyethyl methacrylate.

For a specific, non-limiting example, see Section 19, below.

5 The following working examples are intended to illustrate but not to limit the scope of the present invention.

5.0 EXAMPLE: TRICLOSAN IMPROVES THE SOLUBILITY OF SILVER COMPOUNDS

10 Table 1 illustrates the solubility of the silver salt, silver carbonate, mixed at various molar ratios with ammonia, which is used in a treatment solution, in the absence and the presence of triclosan at various molar ratios. Table 2 illustrates the solubility of the silver salt, silver oxide, mixed at various molar ratios with ammonia in the absence and presence of triclosan at various molar ratios. The solubility results demonstrated in Tables 1 and 2 indicate that silver salts are much
15 more soluble in the presence of triclosan, which suggests that the silver compound and triclosan may form a complex.

 When ammonia and silver carbonate were mixed at a high molar ratio of 400 to 10, the silver salt remained insoluble in the solvent system. In contrast, in the presence of 30 μ mole of triclosan, the molar ratio of ammonia to silver carbonate
20 needed to solubilize was 50 to 10. Achieving a low molar ratio of ammonia to silver salt is preferred because the surface of devices impregnated with a solvent system containing higher amounts of ammonia can be damaged, thereby enhancing the likelihood of microbial adherence to the surface. In the case of silver oxide, only 10 μ mole of ammonia was needed to solubilize more than 90% of 10 μ mole of silver
25 oxide in the presence of 10 μ mole of triclosan. Further, only 20 μ mole of triclosan was needed to completely solubilize 10 μ mole of silver oxide in the presence of only 10 μ mole of ammonia.

TABLE 1

	<u>Silver Carbonate</u> (μ mole)	<u>Ammonia</u> (μ mole)	<u>Triclosan</u> (μ mole)	<u>Solubility</u>
5	10	100	0	Not Soluble
	10	200	0	Not Soluble
	10	300	0	Not Soluble
	10	400	0	Not Soluble
	10	0	30	Not Soluble
10	10	50	10	Partially Soluble
	10	100	10	Partially Soluble
	10	150	10	Soluble
	10	75	20	Partially Soluble
	10	50	30	Soluble

TABLE 2

	<u>Silver oxide</u> (μ mole)	<u>Ammonia</u> (μ mole)	<u>TC (μmole)</u>	<u>Solubility (μmole)</u>
15	10	10	0	Not soluble
	10	100	0	Soluble
	10	10	10	>90% Soluble
20	10	10	20	Soluble

6.0 EXAMPLE: EVALUATION OF THE ANTI-MICROBIAL EFFICACY OF TRICLOSAN-SILVER COMPOUND COMBINATIONS IN BROTH CULTURES

The synergistic anti-microbial efficacy of the triclosan/silver compound combination, triclosan/silver sulfadiazine, is illustrated by the results shown in Table 3, and were determined by the following protocol. Drug solutions containing 10% ammonia were prepared in alcohol, and 0.1 ml of each solution was added to 0.9 ml of bacterial culture (50% trypticase soy broth + 50% Bovine Calf Serum containing 10^8

cfu *S. aureus*/ml). After 10 minutes, a 0.1 ml aliquot was removed and added to 0.9 ml drug inactivating media (LTSB). 0.1 ml from this media was then added to another 0.9 ml of LTSB and 0.2 ml was subcultured on trypticase soy agar plate and incubated at 37°C for 24 hours. The colony counts were then determined. Control
 5 cultures contained similar amounts of ammonia and alcohol as in the test culture.

TABLE 3

	Solution		Growth in Culture
	Triclosan (%)	Silver Sulfadiazine (%)	(cfu/ml)
10	0	0	2.1×10^7
	0.25	0	1.2×10^7
	0.5	0	1×10^7
	0	0.5	5×10^6
	0	1.0	1.5×10^6
15	0.5	0.5	8.3×10^5
	0.5	1.0	1.4×10^4

These results show the synergistic activity of triclosan and silver sulfadiazine. In the control, in the absence of either triclosan or silver sulfadiazine, there was growth in culture of the magnitude of 2.1×10^7 cfu/ml. Comparing the relative reduction of growth in culture by the introduction of triclosan and silver
 20 sulfadiazine, the addition of triclosan alone at 0.25 and 0.5 percent each resulted in a reduction in growth in culture of less than a power of 10 compared to the control. The addition of silver sulfadiazine alone at 0.5 and 1.0 percent each resulted in a 1 log reduction of growth in culture compared to the control.

Comparing the relative reduction of growth in culture by the
 25 introduction of triclosan and silver sulfadiazine in combination, the combination of 0.5 percent triclosan and 0.5 percent silver sulfadiazine resulted in a 2 log reduction in growth in culture compared with the control. The combination of 0.5 percent triclosan and 1.0 percent silver sulfadiazine resulted in a 3 log reduction in cell growth in culture compared with the control. Moreover, the addition of 0.5 percent of silver

sulfadiazine from 0.5 to 1.0 in the presence of 0.5 triclosan resulted in a 1 log reduction in growth in culture, whereas the increase of 0.5 to 1.0 percent silver sulfadiazine in the absence of triclosan did not result in a significant decrease. The cell growth in culture in the presence of 0.5 percent triclosan alone added to the cell growth in culture in the presence of 0.5 percent of silver sulfadiazine, the combined presence of 0.5 triclosan and 1.0 silver sulfadiazine resulted in a 3 log reduction in growth in culture, and the increase of 0.5 to 1.0 percent silver sulfadiazine compared to the growth in culture at .5 percent triclosan results in a 1 log decrease.

The effects of triclosan and silver carbonate combinations on *S. aureus* growth in culture were also determined using the same protocol. The results are presented in Table 4.

TABLE 4

	Solution		Growth in Culture
	Triclosan (%)	Silver Carbonate (%)	(cfu/ml)
15	0	0	5×10^7
	.25	0	2×10^7
	.5	0	1.2×10^7
	0	.06	1×10^5
	0	.125	2×10^3
20	0	.25	5×10^2
	.5	.06	3.2×10^4
	.5	.125	0
	.5	.25	0

The results shown in Table 4 illustrate the synergistic activity of triclosan and silver carbonate. In the control, in the absence of both triclosan and silver carbonate the growth in cell culture was of the magnitude of 5×10^7 cfu/ml. Combining 0.5 percent triclosan and 0.25 percent silver carbonate resulted in a 7 log reduction in growth in culture. The addition of 0.5 percent triclosan alone resulted in a 0 log reduction, and the addition of 0.25 silver carbonate alone resulted in a 5 log reduction. Therefore one would expect a 5 log reduction of growth in cell culture

upon combining the two compositions. However, due to a synergistic activity present when triclosan is combined with silver carbonate an additional 2 log reduction was observed.

Alone, 0.06 percent and 0.125 percent silver carbonate caused a 2 log and a 4 log reduction in growth in culture, respectively, and 0.5 percent triclosan alone caused a 0 log reduction. However, 0.06 percent and 0.125 percent silver carbonate each combined with 0.5 percent triclosan resulted in, respectively, a 3 log reduction and a 7 log reduction of growth in culture.

10 7.0 EXAMPLE: ANTIMICROBIAL EFFICACY OF CATHETERS
 IMPREGNATED WITH (1) TRICLOSAN, SILVER SALTS
 AND VARIOUS ORGANIC ACIDS AND (2) TRICLOSAN,
 SILVER SALTS, AND CHLORHEXIDINE

Catheters impregnated with triclosan, silver compounds and various organic acids, with and without chlorhexidine, were evaluated for effectiveness and duration of antimicrobial efficacy. Treatment solutions comprising triclosan, a silver compound, and an organic acid or chlorhexidine as well as polyurethane polymers were prepared by first dissolving the triclosan, silver compound, and acid or chlorhexidine in methanol, dissolving the polymers in THF, and then mixing the methanol solution with the THF solution in a 30 % v/v methanol solution/70% v/v THF solution solvent system. Polyurethane central venous catheter segments were then dipped for one minute in the treatment solution, then allowed to dry. The final concentrations (percentages based on w/v) of active agents and polymers in the treated catheters are set forth in Table 5.

In related experiments, polyurethane catheter segments were treated by a two-step process. In the first step, catheters were dipped in a 70% v/v THF + 30% v/v reagent alcohol treatment solution having final concentrations of 3% w/v 93A polyurethane and 1% 60D polyurethane, either with or without silver carbonate at a final concentration of 0.6% (the various components were dissolved in either THF or reagent alcohol before mixing the two to produce the treatment solution, as set forth above). The catheters were allowed to dry. Then, in the second step, the catheters were dipped for one minute in a 20% v/v THF + 80% v/v methanol solvent mixture containing either triclosan alone, triclosan and citric acid, or triclosan and

chlorhexidine at concentrations set forth in Table 6.

The zones of inhibition were studied against *S. epidermidis* and *P. aeruginosa* over a two day period. The results, shown in Tables 5 and 6, indicate that the combination of citric acid, triclosan and silver compound (silver carbonate) resulted in superior antimicrobial activity against *Pseudomonas aeruginosa*, compared to other organic acids tested.

TABLE 5

		<u>Zones of Inhibition (mm)</u>			
<u>Treatment Solution</u>		<u><i>S. epidermidis</i></u>		<u><i>P. aeruginosa</i></u>	
		<u>Day 1</u>	<u>Day 2</u>	<u>Day 1</u>	<u>Day 2</u>
10	6% TC + 0.6% Ag ₂ CO ₃ + 3% 93A PU + 1% 60D PU	20	18	9	0
	6% TC + 0.6% Ag ₂ CO ₃ + 2% salicylic acid + 3% 93A PU + 1% 60D PU	20	18	11	0
	6% TC + 0.6% Ag ₂ CO ₃ + 2% mandelic acid + 3% 93A PU + 1% 60D PU	20	18	8	0
15	6% TC + 0.6% Ag ₂ CO ₃ + 2% deoxycholic acid + 3% 93A PU + 1% 60D PU	20	18	8	0
	6% TC + 0.6% Ag ₂ CO ₃ + 2% citric acid + 3% 93A PU + 1% 60D PU	20	19	11	8
20	6% TC + 0.3% Ag ₂ CO ₃ + 2% CHX + 3% 93A PU + 1% 60D PU	21	20	13	12

TABLE 6

			<u>Zones of Inhibition (mm)</u>			
			<u><i>S. epidermidis</i></u>		<u><i>P. aeruginosa</i></u>	
	First Step Treatment Solution	Second Step Treatment Solution	<u>Day</u> <u>1</u>	<u>Day</u> <u>2</u>	<u>Day</u> <u>1</u>	<u>Day</u> <u>2</u>
5	3% 93A PU + 1% 60D PU	6% TC + 4% Citric Acid	20	18	0	0
	3% 93A PU + 1% 60D PU + 0.6% Ag ₂ CO ₃	6% TC	20	18	9	0
	3% 93A PU + 1% 60D PU + 0.6% Ag ₂ CO ₃	6% TC + 4% Citric Acid	20	18	10	7
10	3% 93A PU + 1% 60D PU	6% TC + 2% CHX	21	17	12	11

8.0 EXAMPLE: METHODS OF PREVENTING ADHERENCE ON MEDICAL ARTICLES

The following techniques were used to impregnate 93A polyurethane catheter segments with triclosan and various silver compounds. The resulting surface characteristics, scored on a scale of 1 to 4, with 4 being the most lubricious surface, are shown in Tables 7 and 8. Soaking time varied from 15 seconds to 1 hour.

Method A: The outer surfaces of catheter segments were impregnated by dipping the segments in a treatment solution of 70% v/v THF (containing 93A polyurethane and 60D polyurethane) + 30% v/v (2:1 reagent alcohol:ammonia containing triclosan and silver compound), having final concentrations of 3% w/v 93A polyurethane, 1% w/v 60D polyurethane, 0.3% w/v silver atom or ion, and 6% w/v triclosan.

Method B: Catheter segments had their ends sealed and were soaked for 5 minutes in a treatment solution of 90% v/v (8:1 reagent alcohol/ammonia containing triclosan and silver compound) + 10% THF, having final concentrations of 6% w/v triclosan and 0.3% silver (atom or ion).

Method C: The ends of the catheter segments were sealed and the segments were dipped in a treatment solution of 70% v/v THF (containing 60D polyurethane) + 30% v/v reagent alcohol having a final concentration of 2% w/v 60D polyurethane. The catheter segments were then dried for one hour, and then were
 5 soaked for 5 minutes in a treatment solution of 90% v/v (8:1 ethanol/ammonia containing triclosan and silver compound) + 10% THF, having final concentrations of 6% w/v triclosan and 0.3% silver (the treatment solution used in Method B).

Method D: Catheter segments were dipped in a treatment solution of 70% v/v THF (containing 93A polyurethane and 60D polyurethane) + 30% v/v (2:1
 10 reagent alcohol:ammonia containing a silver compound), having final concentrations of 3% w/v 93A polyurethane, 1% w/v 60D polyurethane, and 0.3% w/v silver (atom or ion) (the treatment solution used in Method A, but without the triclosan).

The surface characteristics of catheter segments treated according to Methods A-D are shown in Table 7.

15

TABLE 7

	<u>Silver Salt</u>	<u>Surface Characteristics</u>			
		<u>A</u>	<u>B</u>	<u>C</u>	<u>D</u>
	0 (only triclosan)	3	3	4	—
	Silver carbonate	4	4	4	3
	Silver deoxycholate	4	4	4	Rough
20	Silver oxide	4	4	4	3
	Silver salicylate	4	4	4	2
	Silver iodide	3	3	3	2
	Silver sulfadiazine	3	2	2	2
	Silver nitrate	4	4	4	4

25

Table 8 shows the results when the outer surfaces of catheter segments were impregnated by dipping the catheters in a treatment solution of 70 % v/v THF (containing 93A and 60D polyurethanes) and 30% v/v reagent alcohol (containing

triclosan, an organic acid, and a silver compound), having final concentrations of 3% w/v 93A polyurethane, 1% w/v 60D polyurethane, 0.3% w/v silver (atom or ion), 6% w/v triclosan, and 1% w/v organic acid.

TABLE 8

5	<u>Metal Salts and Acid in TC Complex</u>	<u>Surface Characteristics</u>
	Silver carbonate + salicylic acid	3.5
	Silver carbonate + deoxycholic acid	3.5
	Silver sulfadiazine + salicylic acid	3
	Silver sulfadiazine + deoxycholic acid	3
10	Silver carbonate + citric acid	4
	Silver sulfadiazine + citric acid	4
	Silver sulfadiazine + palmitic acid	3.5
	Silver sulfadiazine + propionic acid	3.5
	Silver sulfadiazine + aspartic acid	3.5

- 15 9.0 EXAMPLE: ANTI-MICROBIAL POLYURETHANE CATHETERS PREPARED BY A SHORTER SOAKING TIME (15 SECONDS) AND HIGHER TRICLOSAN LEVELS (UP TO 15%) IN THE IMPREGNATION SOLUTION

A shorter soaking time is preferred in a drug/solvent system since it is less likely to negatively affect the physical integrity of a polymeric device, particularly a polyurethane catheter. In order to attain sufficient drug uptake using a shorter soaking time, it is preferred to increase the amount of triclosan in solution to a range of 10% to 15%. For example, polyurethane catheters were dipped in a solution containing 2% 60D polyurethane dissolved in 70% THF + 30% reagent alcohol and allowed to dry for 1 hour. They were then soaked for 15 seconds in a solution prepared by dissolving enough triclosan and AgNO₃ in an 8:1 reagent alcohol/ammonia solution such that when a treatment solution was prepared containing 10% THF and 90% of the reagent alcohol/ ammonia/triclosan/AgNO₃, the treatment solution contained 15 % triclosan and 0.48% AgNO₃. As a comparison, catheters were prepared as above with the following changes: the triclosan

concentration was reduced to 6% and the soaking time was increased to 1 minute. The initial drug levels, measured spectrophotometrically, and zones of inhibition against *S. epidermidis* and *P. aeruginosa* were determined for catheter samples of both groups and are shown in Table 9.

5

TABLE 9

	<u>Treatment</u>	<u>μg TC/cm</u>	<u>Zones of Inhibition (mm)</u>	
			<u>vs. <i>S. epidermidis</i></u>	<u>vs. <i>P. aeruginosa</i></u>
10	15 sec x (15% TC + 0.48% AgNO ₃)	436	11	4
	1 min x (6% TC + 0.48% AgNO ₃)	410	13	4

As illustrated in Table 9, both initial drug uptake and zone of inhibition data indicate that a similar efficacy is obtainable using a higher concentration of drug and a shorter soaking time. In addition, a shorter soaking time in a drug/solvent system is less likely to negatively affect the physical integrity of the device.

15

10.0 EXAMPLE: IMPREGNATION OF TRICLOSAN-SILVER COMBINATION IN LATEX URINARY CATHETER AND PTFE SOFT TISSUE PATCHES (STP)

20

Segments of latex urinary catheters and PTFE soft tissue patches (STP) were impregnated by soaking these materials (or suctioning under vacuum in the case of PTFE STP) for 1 hour in a treatment solution prepared by mixing 80% v/v THF and 10% v/v reagent alcohol/10% v/v ammonia (containing triclosan and silver carbonate), having final concentrations of 1% w/v triclosan and 0.2% w/v silver carbonate. The impregnated materials were dried and then rinsed in water and dried again. The antimicrobial properties of the material were then tested by measuring the zones of inhibition produced against *S. aureus*, *P. aeruginosa*, *E. aerogenes* and *C. albicans* after placing the treated material on a trypticase soy agar plate seeded with

25

0.3 ml of 10^8 cfu/ml bacterial or yeast culture and incubating at 37°C for 24 hours.

The results are shown in Table 10.

TABLE 10

<u>Zones of inhibition (mm)</u>			
5	<u>Urinary Catheter</u>	<u>STP</u>	
	<i>S. aureus</i>	21	>30
	<i>P. aeruginosa</i>	6	7
	<i>E. aerogenes</i>	10	25
	<i>C. albicans</i>	7	12

10 11.0 EXAMPLE: ANTIMICROBIAL EFFICACY OF SUBCUTANEOUS CUFFS CONTAINING FABRICS CONSISTING OF DACRON, ACRYLIC AND PTFE

15 The antimicrobial efficacy of subcutaneous cuff material containing fabrics made of Dacron, Acrylic and PTFE were impregnated with a treatment solution prepared by mixing 10% v/v ammonia/ 10% v/v reagent alcohol (containing silver carbonate, triclosan and chlorhexidine) and 80% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 4% w/v 93A polyurethane, 1% w/v 60D polyurethane, 0.2% w/v silver carbonate, 0.1% w/v triclosan and 0.5% w/v chlorhexidine, The resulting material was then dried for 24 hours and the zones of inhibition against *S. aureus* and *P. aeruginosa* were determined. The zones of inhibition are shown in Table 11.

TABLE 11

25	<u>Cuff Material</u>	<u>Zone of Inhibition (mm)</u>	
		<u><i>S. aureus</i></u>	<u><i>P. aeruginosa</i></u>
	Dacron	20	12
	Acrylic	19	12
	PTFE	18	10

12.0 EXAMPLE: METHOD OF IMPREGNATION OF
LEFT VENTRICULAR ASSIST DEVICE (LVAD) DRIVE LINES

Left ventricular assist device (LVAD) drive lines, which are made of Dacron material and are attached to silicone tubing, were impregnated with a
5 polymeric matrix containing triclosan and silver salts.

Dacron material was treated with one of two different treatment solutions as follows.

In a first case, Dacron material was uniformly spread with a treatment solution which was 10% v/v ammonia, 10% v/v alcohol (containing silver carbonate and triclosan) + 80% THF (containing 93A and 60D polyurethanes), having final
10 concentrations of 0.2% w/v silver carbonate, 0.1% w/v triclosan, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane. As in previous examples, the silver carbonate and triclosan were first dissolved in 1:1 ammonia/alcohol, and the polyurethanes were first dissolved in THF, and then the ammonia/alcohol and THF
15 were mixed to achieve the proper final ratios.

In a second case, Dacron material was uniformly spread with a treatment solution which was 10% v/v ammonia, 10% v/v alcohol (containing silver carbonate, triclosan and chlorhexidine) + 80% THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v silver carbonate, 0.5% w/v
20 chlorhexidine, 0.1% w/v triclosan, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane.

Dacron material having a polymer-drug film prepared as above was then attached to silicone tubing, thereby creating a drive line, and dried. This method is particularly important for devices in which tissue ingrowth is intended to occur after
25 implantation (e.g., cuffs). Antimicrobial activity was evaluated after 24 hours by measuring the zones of inhibition produced by placing 0.25 cm length of drive line on trypticase soy agar seeded with 0.3 ml of 10^8 cfu/ml bacteria and incubated at 37°C for 24 hours. The zones of inhibition were measured after 24 hours, and the results are shown in Table 12.

TABLE 12

<u>Drugs in Catheter</u>	<u>Zones of Inhibition (mm)</u>	
	<u><i>S. aureus</i></u>	<u><i>P. aeruginosa</i></u>
0.2% Ag ₂ CO ₃ , 0.1% TC	16	6
0.2% Ag ₂ CO ₃ , 0.1% TC, 0.5% CHX	20	12

5 As shown in Table 12, drive line treated with polymer, silver carbonate, and low levels of triclosan had antimicrobial activity against both *S. aureus* and *P. aeruginosa*. The antimicrobial effect was improved by the addition of chlorhexidine.

10 In related experiments, subcutaneous cuffs containing fragments consisting of Dacron, acrylic or PTFE were impregnated by dipping in a treatment solution which is 10% v/v ammonia, 10% v/v reagent alcohol (containing silver carbonate, triclosan and chlorhexidine) + 80% THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v silver carbonate, 0.5% w/v chlorhexidine, 0.1% w/v triclosan, 4% w/v 93A polyurethane, and 1% w/v 60D
15 polyurethane. The treated material was allowed to dry, and then tested for antimicrobial activity as set forth above. The results are shown in Table 13.

TABLE 13

<u>Cuff Material</u>	<u>Zone of Inhibition (mm)</u>	
	<u><i>S. aureus</i></u>	<u><i>P. aeruginosa</i></u>
Dacron	20	12
20 Acrylic	19	12
PTFE	18	10

13.0 EXAMPLE: BACTERIAL ADHERENCE ON TRICLOSAN-SILVER COMPOUND IMPREGNATED CATHETERS POST IMPLANTATION IN RATS

25 The ability of catheters impregnated with triclosan and a silver compound to resist bacterial adherence was tested by introducing and maintaining treated catheters *in vivo* in rats, removing the catheters, exposing the catheters to

bacterial cultures, and then measuring the amount of bacteria adhered to the extracted catheter segments.

The catheter segments were impregnated with triclosan and various silver compounds and/or chlorhexidine diacetate (CHA), using treatment solutions having the final concentrations of agents set forth in Table 14, below. In each case, the amount of silver compound in the treatment solution contributed silver atom/ion at a concentration of 0.3% w/v. The treatment solutions comprised THF and reagent alcohol mixed solutions, where polyurethane components were dissolved in the THF and triclosan and silver compounds were dissolved in the reagent alcohol prior to mixing. The amount of THF/polyurethane was generally 70% (v/v). The amount of reagent alcohol was 30% (v/v). Where indicated by an asterisk in Table 16, the solvent was simply reagent alcohol; otherwise, the solvent system was reagent alcohol/ammonia in a 2:1 ratio (accounting for 20% and 10%, respectively, on a volume to volume basis). Polymers in the treatment solutions were initially dissolved in the THF component and had final concentrations of 3% w/v 93A polyurethane and 1% w/v 60D polyurethane. Catheter segments were dipped in the treatment solution, and then dried for three days prior to use. Unimpregnated catheter segments were used as controls.

Six 3 cm segments of catheters from each catheter group were implanted in a subcutaneous pocket on the dorsal side of laboratory rats. After seven days the catheters were removed and rinsed twice in saline and processed as follows: Each group of catheter segments (6 x 3 cm) were transferred to 18 ml of 10% BCS [?]+ 90% TSB containing 3.0ml of 10^7 cfu *S. epidermidis*/ml at 37°C in a rotary shaker for 4 hours. Then the catheters were removed, blotted, rinsed twice in saline, blotted and rolled over the surface of drug neutralizing agar plates (D/E plates) and incubated for 24 hrs at 37°C. The colony counts observed in Table 14 were then determined for each catheter group.

TABLE 14

	Agents In Treatment <u>Solution</u>	No. of Catheter Segments <u>Not Colonized</u>	No. of Catheter Segments <u>Colonized ($10^2 - 10^4$ cfu/cm)</u>
5	6% TC + 0.75% AgSD	0	6
	6% TC + 0.79% Ag paraamino salicylic acid	0	6
10	6% TC + 0.8% Ag acetylsalicylic acid	0	6
	0.75% AgSD + 4% CHA*	0	5
15	6% TC + 0.6% Ag salicylate	1	5
	6% TC + 0.8% Ag laurate	1	5
20	6% TC + 1.5% Ag deoxycholate	1	5
	6% TC	1	4
	6% TC + 0.32% Ag oxide	2	4
25	6% TC + 1% Ag Paraamino benzoic acid	3	3
	6% TC + 0.4% Ag Carbonate	4	2
30	6% TC + 0.48% Ag Nitrate	5	1
	6% TC + 0.4% Ag Carbonate*	5	1
	control 1	0	4
	control 2	1	5
35	* solution does not contain ammonia		

As evidenced from the results of Table 14, the catheter groups containing triclosan-silver salt combinations were effective in preventing bacterial adherence on catheters after being implanted for seven days in rats.

5 A further two sets of experiments were carried out to determine the antimicrobial efficacy of catheters treated according to the invention. In particular, one set of experiments involved an "initial infection model" where the initial catheter wound site was inoculated with bacteria, and another set of experiments involved a "delayed infection model" in which catheters implanted in rats for ten days were removed and exposed to bacterial cultures *in vitro*. In these two sets of experiments,
10 the results of which are shown in Table 15, long term and short term efficacy of treated catheters was evaluated and compared.

In experiments involving the "initial infection model", the dorsal side of a rat was shaved and a 7 cm segment of catheter treated with the agents set forth in Table 15 (with both ends sealed with silicone plugs) was implanted subcutaneously
15 through a 0.5 cm incision just above the shoulder area. The catheter was kept in place, and the tract and insertion site were inoculated with 20 μ l of bacterial culture having 10^8 cfu of *S. aureus* per milliliter. The wound was then closed with surgical clips. After ten days, the catheters were removed and swab cultures of the insertion site and tract were taken. Bacterial adherence on the outer surface of the catheters was
20 determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar plate.

In experiments involving the "delayed infection model", catheter segments (3 cm each, with sealed ends, treated with the agents set forth in Table 15) were implanted subcutaneously in rats (6 segments of catheters treated with the same
25 agents per rat). After ten days *in vivo*, the catheters were excised and rinsed twice with saline. Then each group of six segments was incubated in 18 ml of a log-phase culture of *S. epidermidis* (10^7 cfu/ml of 10% bovine adult serum + 90% TSB) in a rotary shaker for four hours. The bacterial adherence was determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar
30 plate.

Untreated catheters were implanted in rats of both models to serve as controls.

TABLE 15

	Catheter Group	Initial Contamination*	10 Days Post Contamination*
5	Control	1×10^3	$>10^5$
	1.5% CHA + 0.75%AgSD	10	5×10^5
	2% CHA + 2 % TC +0.75% AgSD	0	1×10^4
	6% TC +0.36% AgNO ₃	33	26
10	6% TC +0.4% Ag ₂ CO ₃	90	1×10^2
	6% TC + 0.75% AgSD	Not Done	1×10^4

* colony forming units (cfu) per 1 cm catheter.

As shown in Table 15, triclosan/silver nitrate and triclosan/silver carbonate treated catheter surfaces were found to be more lubricious (as indicated by lower cfu associated with catheters 10 days post-implantation), even though their antimicrobial activity appeared to be lower than that of chlorhexidine/silver sulfadiazine or chlorhexidine/triclosan/silver sulfadiazine treated catheters (as reflected by lower cfu in the initial contamination models). It appears from these results that surface characteristics play an important role in the prevention of delayed infection. Chlorhexidine containing catheters were more effective in preventing initial infections while triclosan/silver compound catheters were more effective in preventing later infections. The latter catheters showed significantly lower bacterial adherence compared to control catheters when infected initially.

14.0 EXAMPLE: ABILITY OF TREATED PTFE PATCHES TO RESIST INFECTION IN AN ANIMAL MODEL

The ability of PTFE soft tissue patches, treated with combinations of triclosan and/or chlorhexidine and the silver salt, silver carbonate, to resist infection was tested as follows. Disks of PTFE patches were impregnated with treatment solutions prepared by dissolving triclosan and/or chlorhexidine and silver carbonate in

1:1 reagent alcohol/ammonium hydroxide, and then mixing with THF to produce a 80% v/v THF, 10% reagent alcohol, 10% v/v ammonium hydroxide solution having triclosan, chlorhexidine, and silver carbonate final concentrations as specified in Table 16 below. The patch material was soaked in treatment solution for 1 hour under a vacuum. The patches were implanted subcutaneously in a pocket in the abdominal area of rats and infected with $10 \mu\text{l}$ of 10^8 CFU *S. aureus*. After 7 days, they were removed and bacterial adherence was determined by sonicating the catheters in drug neutralizing media and then subculturing on a trypticase soy agar plate. The efficacy of patches in resisting infection due to contamination at the time of implantation is illustrated by the bacterial adherence data provided in Table 16.

TABLE 16

<u>Impregnation Solution</u>	<u>Bacterial Adherence</u> <u>CFU/DISK</u>
0.25%TC + 0.2%Ag ₂ CO ₃ +0.5 CHX	4
1.0%TC + 0.2%Ag ₂ CO ₃	1
0.5%CHX + 0.2%Ag ₂ CO ₃	15
0.5%TC + 0.25%CHA + 0.25%CHX	15
Unimpregnated	7.6×10^3

As shown in Table 16, all of the above groups with and without chlorhexidine were observed to be similarly efficacious relative to the control, unimpregnated group.

15.0 EXAMPLE: ENHANCEMENT OF THE
ANTI-MICROBIAL ACTIVITY OF DEVICES
CONTAINING SILVER AND TRICLOSAN
USING OTHER SOLUBLE ANTI-INFECTIVE AGENTS

Polyurethane catheter segments were impregnated by dipping in a treatment solution prepared by mixing 10%v/v ammonia/20%v/v reagent alcohol (containing triclosan, silver carbonate, and, except for the control, an additional antibiotic) with 70% v/v THF (containing 93A and 60D polyurethanes), having final

concentrations of 3% w/v 93A polyurethane, 1% w/v 60D polyurethane, 6% w/v triclosan, 0.4% w/v Ag_2CO_3 and 0.5% of the antibiotics set forth in Table 17, below. The treated catheter segments were then dried for 24 hours and evaluated for antimicrobial activity by determining the zones of inhibition created in cultures of various microbes. The antimicrobial properties of the material were then tested by measuring the zones of inhibition produced against *S. aureus*, *P. aeruginosa*, *E. aerogenes* and *C. albicans* after placing the treated material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial/yeast culture and incubating at 37°C for 24 hours.

Table 17 shows the enhanced effective broad spectrum anti-microbial field around a catheter produced by the addition of soluble anti-infective agents. Using antibiotics along with the triclosan-silver salt combination may reduce the risk of development of antibiotic resistant microbes.

TABLE 17

	Agents in Treatment Solution	Zones of Inhibition (mm)			
		<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>E. aerogens</i>	<i>C. albicans</i>
15	6% TC + 0.4% Ag_2CO_3 + 0.5% Gramicidin	14	6	7	7
20	6% TC + 0.4% Ag_2CO_3 + 0.5% Polymixin	17	16	15	7
	6% TC + 0.4% Ag_2CO_3 + 0.5% Norfloxacin	19	18	18	10
25	6% TC + 0.4% Ag_2CO_3 + 0.5% Sulfamylon	12	12	13	9
	6% TC + 0.4% Ag_2CO_3 + 0.5% Rifampicin	21	5	5	0
30	6% TC + 0.4% Ag_2CO_3 + NO ANTIBIOTIC (CONTROL)	13	6	6	5

16.0 EXAMPLE: ANTIMICROBIAL ACTIVITY OF VARIOUS
TRICLOSAN - SILVER COMPOUND COMBINATIONS

5 Polyurethane catheter segments were treated by dipping in a treatment solution having final concentrations of triclosan and/or silver compound as set forth in Table 11, below. Six catheter segments from each group were placed vertically on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial/yeast culture and incubated at 37°C for 24 hours. The results are shown in Table 18.

TABLE 18

		<u>Zones of Inhibition (mm)</u>			
	<u>Drug in Impregnation Solution</u>	<u>S. aureus</u>	<u>P. aeruginosa</u>	<u>Enterobacter aerogenes</u>	<u>Candida albicans</u>
5	6% TC	15	0	6	0
	1% AgSD	8	5	0	0
	0.5% Ag ₂ CO ₃	8	7	0	6
	0.6% AgSalicylate	9	6.5	0	7.3
	0.32% Ag Oxide	9	7	0	11
10	1.5% Ag Deoxycholate	1	4	0	5
	6% TC + 1% AgSD	17	6	5	5
	6% TC + 0.5% Ag ₂ CO ₃	22	9	6	7
	6% TC + 0.6% Ag Salicylate	20	10	7	11
15	6% TC + 0.32% Ag Oxide	22	10	6	15
	6% TC + 1.5% Ag Deoxycholate	17	7	5	10
	2% TC + 1% AgSD + 2% CHX	17	11	12	13
20	6% TC + 0.7% Ag ParaaminoBenzoate acid	17	7	6	5
	6% TC + 0.79% Ag Paraamino Salicylate	19	7	6	4
	6% TC + 0.8% Ag AcetylSalicylate	19	8	7	9
25	0.7% Ag Paraamino Benzoate	3.5	4.0	0	0
	0.79% Ag ParaaminoSalicylate	5.5	7.5	3.3	0
	0.8% Ag Acetyl Salicylate	7.0	8.0	4.7	0

It is noted that the combination of triclosan with either silver paraaminobenzoate, silver paraaminosalicylate, or silver acetylsalicylate resulted in unexpected efficacy against *C. albicans* as compared with each of the agents tested alone. Also illustrated by Table 18 is the synergistic effect achieved by the presence of triclosan in combination with silver salts.

17.0 EXAMPLE: IMPREGNATION OF ANTI-INFLAMMATORY AGENTS ALONG WITH TRICLOSAN AND SILVER SALTS

The following experiments demonstrated that the addition of the anti-inflammatory agent salicylic acid and its derivatives to combinations of triclosan and silver compounds improved antimicrobial activity.

LVAD drive lines made of Dacron were impregnated with triclosan, silver sulfadiazine and chlorhexidine, with or without salicylic acid, as follows. One set of pieces of Dacron were uniformly spread with a treatment solution prepared by mixing 30% v/v alcohol (containing triclosan (TC), silver sulfadiazine (AgSD), and chlorhexidine (CHX)) and 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 0.1% w/v triclosan, 0.2% w/v silver sulfadiazine, 0.5% w/v chlorhexidine, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane. Another set of Dacron pieces were uniformly spread with a second treatment solution having the same components, but also having a final concentration of 0.5% w/v salicylic acid (the salicylic acid being initially dissolved in the ethanol component). As a control, one set of Dacron pieces was treated with a third treatment solution containing salicylic acid and polymer but lacking triclosan, silver sulfadiazine, and chlorhexidine. The Dacron pieces were dried for 24 hours prior to antimicrobial testing.

In an analogous set of experiments, polyurethane catheters were impregnated with triclosan and silver carbonate, with or without salicylic acid or one of its derivatives. One set of polyurethane catheter segments were therefor dipped in a treatment solution prepared by mixing 20% v/v reagent alcohol/10% v/v ammonia (containing triclosan and silver carbonate) and 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 6% w/v triclosan, 0.4% w/v silver carbonate, 3% w/v 93A polyurethane and 1% w/v 60D polyurethane. Three other sets

of catheter segments were treated with the same solution further having a final concentration of 0.5% w/v salicylic acid, 0.5% w/v acetylsalicylic acid, or 0.5% w/v paraaminosalicylic acid, respectively (the salicylic acid or derivative thereof being first dissolved in the ethanol/ammonia solution). As controls, another three sets of catheters were impregnated using treatment solutions as above, containing either 0.5% w/v salicylic acid, 0.5% w/v acetylsalicylic acid, or 0.5% w/v paraaminosalicylic acid and polymer, but lacking triclosan or silver carbonate. The treated catheters were dried for 24 hours prior to antimicrobial testing.

Antimicrobial testing was performed by placing the Dacron drive line or catheter segment on trypticase soy agar seeded with 5×10^8 cfu of *Pseudomonas aeruginosa*. The zones of inhibition were measured after incubation of the plates at 37°C for 24 hours. The results, presented in Table 19, illustrate that both hydrophilic (polyurethane) and hydrophobic (Dacron) medical devices can be rendered infection resistant and that anti-inflammatory agents such as salicylates enhance antimicrobial activity.

TABLE 19

Agents in Treatment Solution	Zones of Inhibition (mm) against <i>P. aeruginosa</i>	
	<u>LVAD DriveLine</u>	<u>Polyurethane Catheters</u>
0.1% TC + 0.2% AgSD + 0.5% CHX	12	-
0.1% TC + 0.2% AgSD + 0.5% CHX + 0.5% Salicylic acid	15	-
0.5% Salicylic Acid	0	-
6% TC + 0.4% Ag ₂ CO ₃	-	7
6% TC + 0.4% Ag ₂ CO ₃ + 0.5% Salicylic Acid	-	11
6% TC + 0.4% Ag ₂ CO ₃ + 0.5% Acetylsalicylic Acid	-	11
6% TC + 0.4% Ag ₂ CO ₃ + 0.5% Paraaminosalicylic Acid	-	11

Agents in Treatment Solution	Zones of Inhibition (mm) against <i>P. aeruginosa</i>	
	<u>LVAD DriveLine</u>	<u>Polyurethane Catheters</u>
0.5% Salicylic Acid	-	0
0.5% Acetylsalicylic Acid	-	0
0.5% Paraaminosalicylic Acid	-	0

5 18.0 EXAMPLE: ANTI-MICROBIAL EFFICACY OF COMBINATIONS
OF SILVER SALTS AND CHLORINATED PHENOLIC
COMPOUNDS

10 Silver compounds, in particular silver salts and various phenolic
compounds were combined to study prolonged anti-microbial efficacy of the various
compositions. Catheter segments for study were prepared by treating a polyurethane
catheter segment in a solution of 3% 93A polyurethane and 1% 60D polyurethane,
having final concentrations of agents set forth in Table 20. Then segments were placed
on petri dishes seeded with *Pseudomonas aeruginosa*. Table 3 illustrates the zones of
inhibition of *Pseudomonas aeruginosa* over a three day period of Ag_2CO_3 and Ag_2CO_3
15 in combination with three phenolic compositions, (1) parachlorometaxylenol
(PCMX), (2) o-phenyl phenol and (3) p-tertiary amyl phenol, and compared their
respective efficacy to triclosan and Ag_2CO_3 . As shown in Table 20 it appears that a
synergistic effect occurs when chlorinated phenols are combined with silver salt
exhibiting prolonged anti-microbial activity.

TABLE 20

	<u>Drugs in Catheter</u>	<u>Zones of Inhibition (mm)</u>		
		DAY <u>1</u>	<u>2</u>	<u>3</u>
	6% triclosan + 0.6% Ag ₂ CO ₃	11	10	6
5	6% PCMX + 0.6% Ag ₂ CO ₃	12	10	7
	6% o-phenyl phenol + 0.6% Ag ₂ CO ₃	10	0	0
	6% p-tertiary amyl phenol + 0.6% Ag ₂ CO ₃	10	0	0
	0.6% Ag ₂ CO ₃	10	0	0

10 19.0 ANTIMICROBIAL EFFICACY OF HYDROPHILIC
OR HYDROPHOBIC MATRIX SYSTEMS BY
ADDITION OF HYDROGEL POLYMER

We tested the effect on antimicrobial activity of adding a hydrogel polymer such as polyvinyl pyrrolidone (PVP) to treatment solutions containing triclosan, silver compound, and polyurethanes, and then using such solutions to treat
15 medical devices. Polyurethane catheter segments were dipped in one of the following two treatment solutions:

(i) a treatment solution prepared by mixing 30% v/v reagent alcohol (containing triclosan and silver carbonate) with 70% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 6% w/v triclosan, 0.4% w/v silver
20 carbonate, 3% w/v 93A polyurethane, and 1% w/v 60D polyurethane; or

(ii) a treatment solution prepared by mixing 30% v/v reagent alcohol (containing triclosan and silver carbonate) with 70% v/v THF (containing 60D polyurethane and PVP), having final concentrations of 6% w/v triclosan, 0.4% w/v silver carbonate, 3% w/v 60D polyurethane, and 2% w/v PVP.

25 The treated catheter segments were then dried for 24 hours and then tested for antimicrobial activity by measuring the zones of inhibition The antimicrobial properties of the material were then tested by measuring the zones of inhibition produced against *S. epidermidis* and *P. aeruginosa* after placing the treated

material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial culture and incubating at 37°C for 24 hours.. In addition, the amount of triclosan present per centimeter of catheter was determined spectrophotometrically. The results are shown in Table 21.

5

TABLE 21

	<u>Compounds in Treatment Solution</u>	<u>µg TC/cm</u>	<u>Zones of Inhibition (mm)</u>	
			<u>vs. <i>S. epidermidis</i></u>	<u>vs. <i>P. aeruginosa</i></u>
	6% TC + 0.4% Ag ₂ CO ₃ + 3% 93A PU + 1% 60D PU	425	11	6.5
10	6% TC + 0.4% Ag ₂ CO ₃ + 3% 60D PU + 2% PVP	397	18	10

In other experiments, the effect of PVP incorporated into a hydrophobic article, *i.e.*, Dacron material for LVAD drive lines, was determined. In particular, pieces of Dacron were uniformly spread with one of the two following treatment solutions:

(iii) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, and 1% w/v 60D polyurethane, or

(iv) a treatment solution prepared by mixing 10% v/v reagent alcohol (containing triclosan, chlorhexidine diacetate (CHA), chlorhexidine free base (CHX) and silver sulfadiazine) with 90% v/v THF (containing 93A and 60D polyurethanes and PVP and polyvinylchloride ("PVC")), having final concentrations of 0.2% w/v triclosan, 0.3% w/v chlorhexidine diacetate, 0.2% w/v chlorhexidine free base, 0.2% w/v silver sulfadiazine, 4% w/v 93A polyurethane, 1% w/v 60D polyurethane, 2% w/v PVP and 4% w/v PVC.

The treated Dacron was allowed to dry for 24 hours and then attached to the outer surface of silicon tubing using a silicon adhesive to produce a drive line. The resulting drive lines were then tested for antimicrobial activity by measuring the zones of inhibition produced against *S. epidermidis*, *P. aeruginosa*, and *C. albicans* after placing the treated material on a trypticase soy agar plate seeded with 0.3 ml of 10^8 cfu/ml bacterial or yeast culture and incubating at 37°C for 24 hours. In addition, the amounts of triclosan and chlorhexidine present per centimeter of Dacron were determined spectrophotometrically. The results are shown in Table 22.

TABLE 22

Group	$\mu\text{g TC/cm}$	$\mu\text{g CHX/cm}$	Zones of Inhibition (mm)		
			<i>v. S. epidermidis</i>	<i>v. P. aeruginosa</i>	<i>v. C. albicans</i>
LXI	387	662	17	11.5	14
LXII	420	480	22	15	16

As illustrated in Tables 21 and 22, the use of a hydrogel such as PVP in a hydrophilic (*e.g.*, polyurethane) or hydrophobic (*e.g.*, PVC) matrix allows better drug release as evidenced by greater zones of inhibition.

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

CLAIMS

1. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver salt and between about 0.1
5 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidine or a chlorhexidine salt.
2. The anti-infective medical article of claim 1, where the treatment solution further comprises an organic acid at a concentration of between about 0.1 and 5 percent.
- 10 3. The anti-infective medical article of claim 2, where the organic acid is citric acid.
4. The anti-infective medical article of claim 1, where the treatment solution further comprises an anti-inflammatory agent, at a concentration of between about 1 and 5 percent.
- 15 5. The anti-infective medical article of claim 4, where the anti-inflammatory agent is salicylic acid or a derivative thereof.
6. The anti-infective medical article of claim 1, where the treatment solution further comprises an additional antimicrobial agent.
- 20 7. The anti-infective medical article of claim 6, where the additional antimicrobial agent is selected from the group consisting of gramicidin, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

8. The anti-infective medical article of claim 1, where the treatment solution further comprises between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer.

5 9. The anti-infective medical article of claim 1 which is a polytetrafluoroethylene patch.

10 10. A polymer-containing vascular catheter comprising between about 100 and 600 micrograms of triclosan per centimeter and between about 25 and 100 micrograms of silver per centimeter, where the catheter does not contain chlorhexidine or a chlorhexidine salt.

10 11. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver salt and between about 0.1 and 20 percent triclosan, where the treatment solution and the medical article do not contain chlorhexidine or a chlorhexidine salt.

15 12. The method of claim 11, where the treatment solution further comprises an organic acid at a concentration of between about 0.1 and 5 percent.

13. The method of claim 12, where the organic acid is citric acid.

20 14. The method of claim 11, where the treatment solution further comprises an anti-inflammatory agent, at a concentration of between about 1 and 5 percent.

15. The method of claim 14, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

16. The method of claim 11, where the treatment solution further comprises an additional antimicrobial agent.

17. The method of claim 14, where the additional antimicrobial agent is selected from the group consisting of gramiciain, polymixin, norfloxacin, sulfamylon,
5 polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

18. The method of claim 11, where the treatment solution further comprises between about 1 and 5 percent of one or more hydrophilic or hydrophobic polymer.

19. The method of claim 11, where the polymer-containing medical article
10 is a polytetrafluoroethylene patch.

20. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.3 and 1.5 percent of a silver compound and between about 0.1 and 20 percent of a chlorinated phenol, where the chlorinated phenol is not
15 triclosan.

21. The anti-infective medical article of claim 20, where the chlorinated phenol is parachlorometaxilenol.

22. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution
20 comprising between about 0.1 and 5 percent of a metal compound, between about 0.1 and 20 percent triclosan, and between about 0.5 and 10 percent of a hydrogel.

23. The anti-infective medical article of claim 22, where the metal compound is a silver compound.

24. The anti-infective medical article of claim 22, where the hydrogel comprises polyvinyl pyrrolidone.

25. An anti-infective medical article prepared by exposing a polymer-containing medical article, for an effective period of time, to a treatment solution
5 comprising between about 0.1 and 5 percent of a silver compound, between about 0.1 and 20 percent of triclosan, and between about 1 and 5 percent of an anti-inflammatory agent.

26. The anti-infective medical article of claim 25, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

10 27. The anti-infective medical article of claim 25, where the treatment solution further comprises an additional antimicrobial agent.

28. The anti-infective medical article of claim 27, where the additional antimicrobial agent is selected from the group consisting of chlorhexidine, a chlorhexidine salt, gramicidin, polymixin, norfloxacin, sulfamylon,
15 polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

29. The anti-infective medical article of claim 25 which is a polytetrafluoroethylene graft.

30. A method of preparing an anti-infective medical article, comprising exposing a polymer-containing medical article, for an effective period of time, to a
20 treatment solution comprising between about 0.3 and 1.5 percent of a silver compound and between about 0.1 and 20 percent of a chlorinated phenol, where the chlorinated phenol is not triclosan.

31. The method of claim 30, where the chlorinated phenol is parachlorometaxlenol.

32. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.1 and 5 percent of a metal compound, between about 0.1 and 20 percent triclosan, and between about 0.5 and 10 percent of a hydrogel.

33. The method of claim 32, where the metal compound is a silver compound.

34. The method of claim 32, where the hydrogel comprises polyvinylpyrrolidone.

35. A method of preparing an anti-infective medical article comprising exposing a polymer-containing medical article, for an effective period of time, to a treatment solution comprising between about 0.1 and 5 percent of a silver compound, between about 0.1 and 20 percent of triclosan, and between about 1 and 5 percent of an anti-inflammatory agent.

36. The method of claim 35, where the anti-inflammatory agent is salicylic acid or a derivative thereof.

37. The method of claim 35, where the treatment solution further comprises an additional antimicrobial agent.

38. The method of claim 34, where the additional antimicrobial agent is selected from the group consisting of chlorhexidine, a chlorhexidine salt, gramicidin, polymixin, norfloxacin, sulfamylon, polyhexamethylene biguanide, alexidine, benzalkonium chloride and rifampicin.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08692

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61L29/16 A61L27/54 A61L31/16 A61L17/00 A61L15/44
A61L2/18 //A61L101:02,A61L101:32,A61L101:34,A61L101:42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 25085 A (COLUMBIA UNIVERSITY OF THE CIT :MODAK SHANTA (US); SAMPATH LESTER) 17 July 1997 (1997-07-17) cited in the application page 13, line 23 -page 14, line 8 page 14, line 26 - line 36 claims ----	1,2, 6-11, 16-19, 22,23, 32,33
X	EP 0 663 212 A (HYDROMER INC) 19 July 1995 (1995-07-19) claims ----	1,2,4-6, 8,11,12, 14-16,18
X	WO 96 22114 A (VITAPHORE CORP) 25 July 1996 (1996-07-25) page 13, line 2 - line 13 claims 1-3,5,6,9,12-16 ----	1,10,11
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 July 2000

Date of mailing of the international search report

17/07/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Thornton, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08692

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 05, 31 May 1999 (1999-05-31) & JP 11 049625 A (LION CORP), 23 February 1999 (1999-02-23) abstract	1
A	US 5 357 636 A (DANGMAN KENNETH H ET AL) 25 October 1994 (1994-10-25) claims	1-9, 11-38
A	EP 0 472 413 A (BECTON DICKINSON CO) 26 February 1992 (1992-02-26) page 5, line 37 -page 6, line 13 -----	1,4-8, 10,11, 14-18, 20-23, 25-31, 35-38

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 00/08692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9725085 A	17-07-1997	US 5772640 A AU 1523597 A CA 2241461 A EP 0874655 A	30-06-1998 01-08-1997 17-07-1997 04-11-1998
EP 0663212 A	19-07-1995	US 5420197 A AT 165011 T AU 682415 B AU 8038294 A CA 2138351 A DE 69502029 D DE 69502029 T ES 2117825 T JP 7250886 A	30-05-1995 15-05-1998 02-10-1997 20-07-1995 14-07-1995 20-05-1998 03-12-1998 16-08-1998 03-10-1995
WO 9622114 A	25-07-1996	AU 4763696 A CA 2210119 A EP 0804256 A JP 11500330 T	07-08-1996 25-07-1996 05-11-1997 12-01-1999
JP 11049625 A	23-02-1999	NONE	
US 5357636 A	25-10-1994	NONE	
EP 0472413 A	26-02-1992	US 5102401 A AT 140871 T AU 642737 B AU 7724991 A CA 2043051 C DE 69121146 D DE 69121146 T ES 2092548 T JP 2056356 C JP 4226670 A JP 7096026 B KR 9405303 B	07-04-1992 15-08-1996 28-10-1993 27-02-1992 22-11-1994 05-09-1996 06-02-1997 01-12-1996 23-05-1996 17-08-1992 18-10-1995 16-06-1994